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Ramon Berguer

Roger F. Smith

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This negative report, based on statistical analysis of three distinct groups, contradicts some previously-held conclusions in the field of hypertension.—Ed.

Angiotensin Infusion:

A Clinical Evaluation as a Screening Test for Renovascular Hypertension

By Ramon Berguer, M.D.* and Roger F. Smith, M.D.**

Introduction

In 1963 Kaplan and Silah[6] suggested that hypertensive patients could be classified according to their blood pressure response to an infusion of angiotensin II. They reported a lower pressor response in patients having renovascular hypertension than in those having hypertension of the so-called essential type.[7,8] The physiological rationale for this test has been enunciated as follows: patients with hypertension secondary to renal artery stenosis are expected to have high levels of endogenous angiotensin because of their high renin output. Either due to saturation of the end-organ with large amounts of endogenous angiotensin or due to elevated titers of angiotensinases, little effect is to be expected from the injection of exogenous angiotensin II. The blood pressure response in renovascular hypertensives to an infusion of angiotensin, therefore, should be small.

Later work in this field revealed that the lesser type of response was also observed in patients with malignant hypertension and in other conditions associated with secondary hyperaldosteronism. A number of published papers dealing with the pressor response to angiotensin infusion present contradictory observations and conclusions as to its clinical usefulness as a screening test.[1,4,9] We undertook the present study in an attempt to verify whether the angiotensin infusion test could be of value in separating patients with renovascular hypertension from patients with other types of non-malignant hypertension.

*Resident, Department of General Surgery.
**Chief of Division II, Department of General Surgery.
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Table I

Case Material

Groups	No. of patients	Age (mean and s.d. values)
I (renovascular)	6	53.7 ± 7.3
II (essenti. hypert.)	13	51.9 ± 8.3
III (control)	14	20.6 ± 6.2

Materials and Methods

As shown in Table I, three groups of patients were studied. Group 1 included six renovascular hypertensives. All six patients had established diastolic hypertension (basal diastolic pressure greater than 90 mm Hg), stenosis of the renal artery or arteries proved by arteriography and, later on, successful arterioplasties with good clinical results (Figs. 1, 2 and 3).

Group 2 was formed by 13 hypertensives in whom clinical and radiological data could rule out a specific etiology. Sixty percent of them had arteriograms confirming the negative results of routine rapid sequence IVU and ^{131}I renograms. None of the patients in group 1 or 2 had malignant hypertension or evidence of secondary hyperaldosteronism.

Group 3 was the control group. It was formed by 14 young people without hypertension or evidence of any other disease.

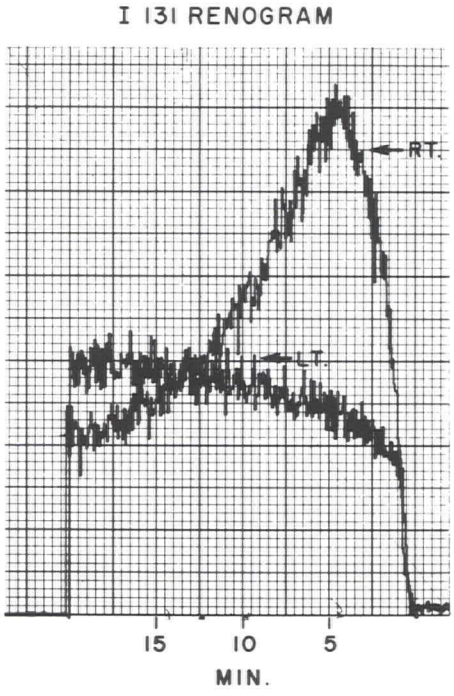

Figure 1

Renovascular hypertension. Typical ^{131}I renogram showing delayed pick-up in the left kidney tracing.

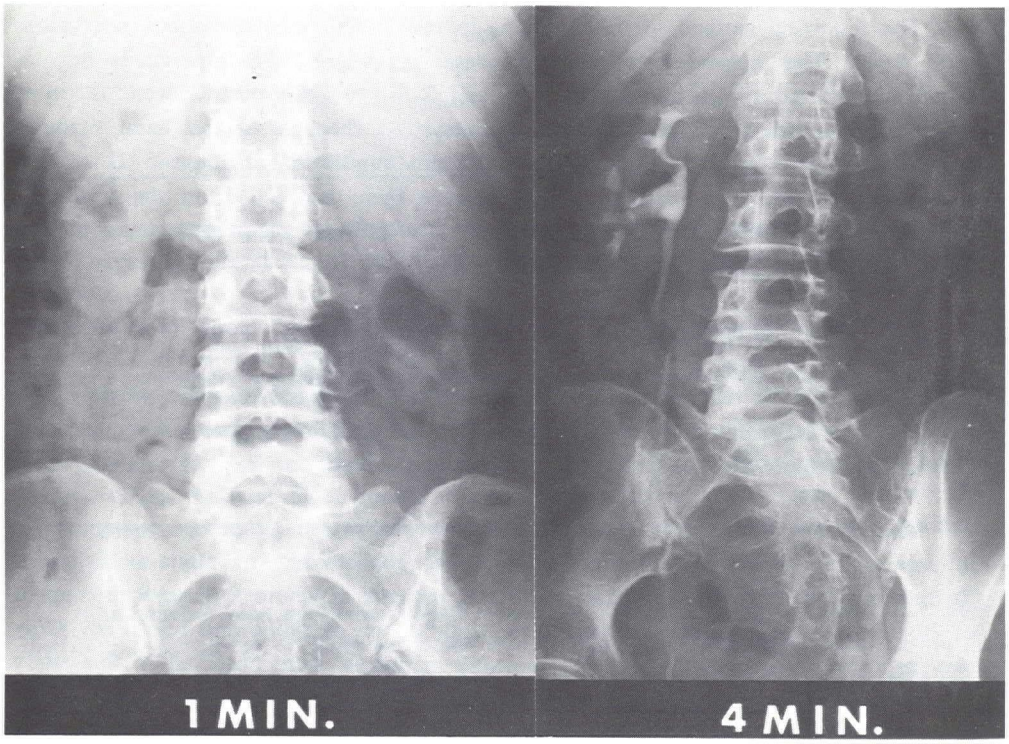

Figure 2

Same patient as in Fig. 1. Typical rapid sequence IVU demonstrating delayed function in the left kidney.

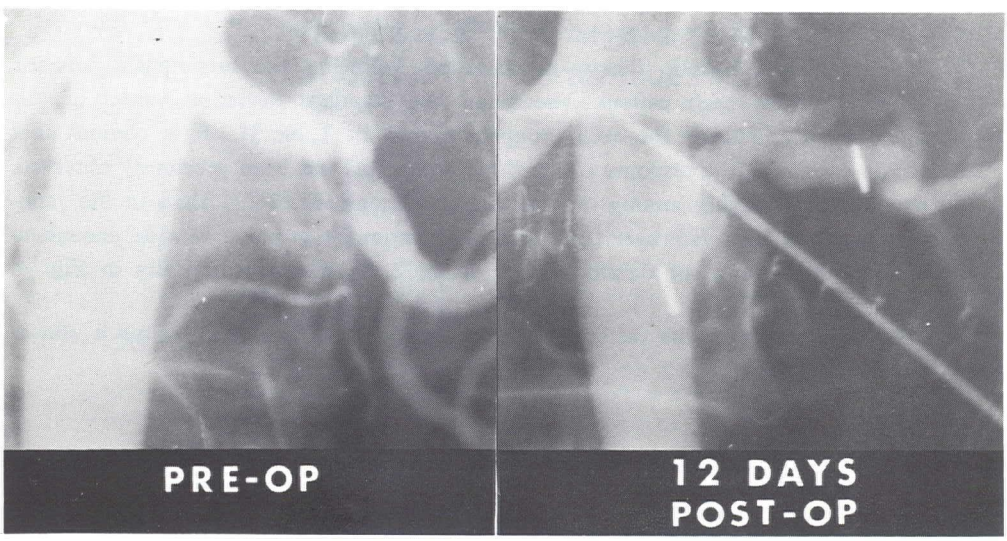

Figure 3

Same patient as in Fig. 1. Preoperative arteriogram showing the left renal artery stenosis and postoperative arteriogram showing patent aortorenal bypass.

The following method of infusion was followed: No medicamentous restrictions were made. The patients were placed at basal conditions. An intravenous drip of saline was started in an antecubital vein and basal blood pressures were recorded every five minutes for a period of 25 minutes. At the end of the basal readings the patients were infused 4 nanograms/kilogram/minute of angiotensin II over a five-minute period. The diastolic pressures were then recorded from the beginning of the infusion every minute for six minutes. The patients received a mean of 160 ml of saline prior to the angiotensin infusion.

The lowest diastolic reading obtained during the basal blood pressure determinations was considered to be the basal diastolic pressure. The difference between the highest diastolic reading during the infusion and the basal diastolic pressure was interpreted as the maximal diastolic increment observed following the standard infusion dose of angiotensin II.

Kaplan and Silah reported no alterations in the pressor response to angiotensin in patients receiving oral reserpine, hydralazine, guanethidine or alpha-methyldopa.[8] To rule out salt depletion as a factor of error, patients in whom a diastolic increment of 20 mm Hg was not obtained were given 250-300 ml of saline and reinfused. Only two instances of a moderately higher diastolic increment were observed in this study following reinfusion after 250-300 ml of saline. This increase did not significantly affect the statistical analysis of the groups. Therefore our data refer to the standard infusion of 4 nanograms/kilogram/minute in all patients. Our results agree with other workers using patients with normal salt intake and not on diuretics.[5]

Results

The maximal diastolic increment recorded following the angiotensin infusion was determined for each patient. The mean and standard deviation values of this increment were computed for each group as shown in Table II. It is obvious that there is an overlap in the response of the three groups. As has been previously observed, the mean value is higher among the essential hypertensives (26.8) than in the renovascular group (25.0). However the standard deviation of group 1 is wide enough to include the entire range of distribution of group 2, as shown graphically in Fig. 4.

The significance of the difference in the response of the three groups is shown in Table III.

Table II

Maximal diastolic increment during angiotensin infusion.

Group	Mean value (mm Hg)	St. deviation
I	25.0	±16.6
II	26.8	±12.5
III	23.0	± 8.2

Angiotensin Infusion

Table III

P values obtained by comparison of the 3 groups

Group 1	versus	Group 2	: 0.82
Group 1	versus	Group 3	: 0.80
Group 2	versus	Group 3	: 0.36

It is meaningful that the highest value of P occurs when the values of group 1 are compared with those of group 2, precisely the two groups that need to be separated.

Because of the small size of the samples involved the diastolic increment within each group, and that of the three groups, were submitted to Weibull statistical analysis.

Concerning the pressor response to angiotensin, there was a 95% confidence difference between the basal and the maximal diastolic readings in the renovascular and control groups (Figs. 5A and 5C). In the essential hypertensive group there was overlap in the response among those patients who had initial high basal diastolic readings (Fig. 5B).

Simultaneous plotting of the pressor response in the three groups shows a unimodal distribution for group 3. This we would expect from a control population. Group 1 (renovascular) is rather homogeneous with the exception of one value (the possibility of this being a false value can be considered). The essential hypertension group is irregular and heterogeneous and its plotting crosses the renovascular group making their distinction impossible (Fig. 6).

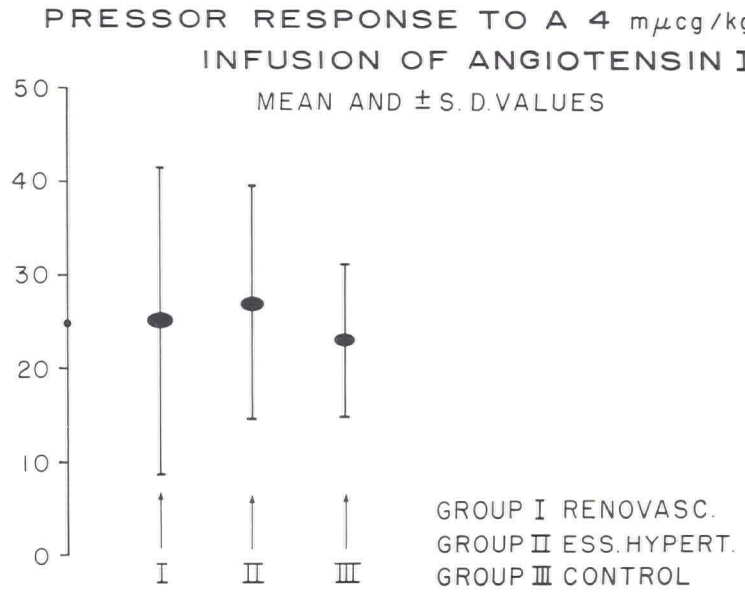

Figure 4

Diagram showing the maximal diastolic increment to the angiotensin infusion in each group.

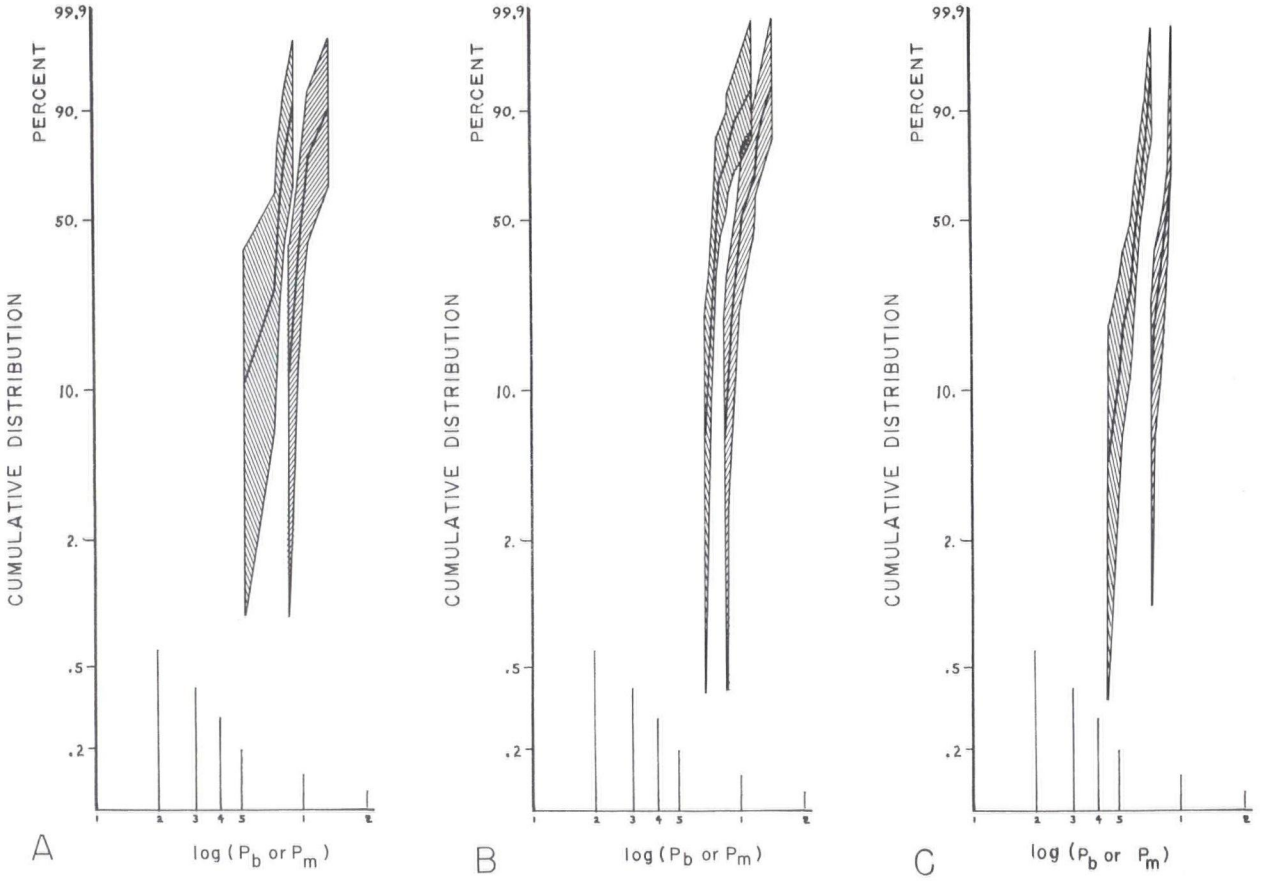

Figure 5

Weibull plotting of the basal and of the maximal diastolic infusion values for (A) renovascular group, (B) essential hypertension group and (C) control group (P_b = basal diastolic value; P_m = maximal diastolic value).

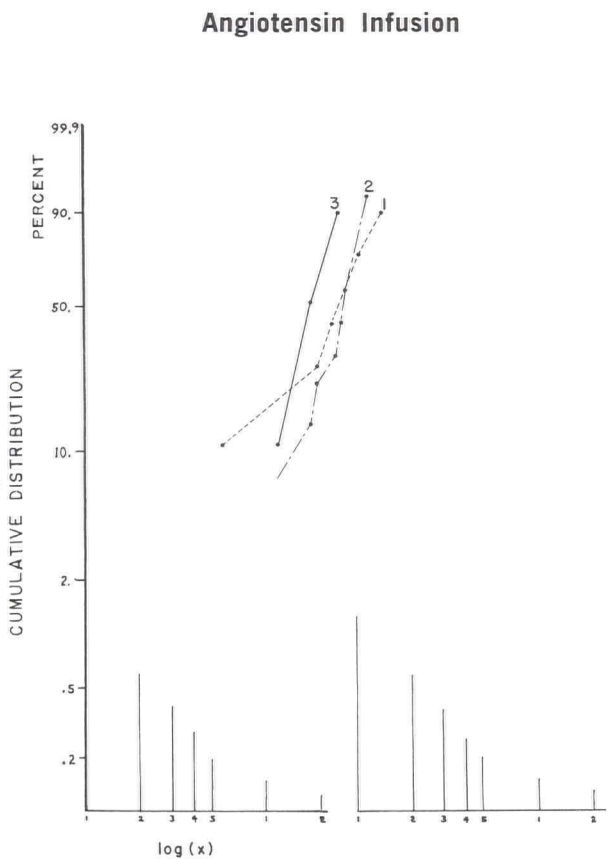

Figure 6

Weibull plotting of the pressor response of each of the three groups to the angiotensin infusion (x = maximal diastolic increment to the angiotensin infusion).

Discussion

It is commonly admitted that renovascular hypertensives have increased plasma levels of renin and angiotensin. The pressor effect of the latter is believed to be responsible for the hypertension of these patients. The renin-angiotensin pressor mechanism is thought by many to be a pathological manifestation occurring within a larger physiological set: the renin-angiotensin-aldosterone system, whose main action is thought to be the maintenance of an adequate blood volume.[2] Admittedly all steps are not clear and other factors must be implicated to explain the absence of hyperaldosteronism in a significant number of patients with renovascular hypertension or the existence of a paradox such as Bartter's syndrome where hyperplasia of the juxtaglomerular apparatus, increase in angiotensin levels, and hyperaldosteronism coexist with a normal blood pressure.

The mechanisms of renovascular hypertension may not be so simple. The participation of the renomedullary prostaglandins in renocortical ischemia and sub-

sequent hypertension is yet to be determined. Another factor to be taken into account concerning the pressor effect of angiotensin is that it increases the levels of circulating catecholamines, with epinephrine increased more than norepinephrine.[10] In spite of these unanswered problems there is seemingly enough evidence to indicate that increased production of angiotensin is a responsible factor in renovascular hypertension.

The theory behind the angiotensin infusion test implies that the angiotensin effect is specific. But this assumption can also be challenged. It has been reported that renovascular hypertensives have a lesser response to phenyllysine vasopressin than do essential hypertensives.[9] Much the same response is assumed to occur with angiotensin infusion. In either of these two groups we have not found a statistically significant difference between the responses to a cold pressor test and to an angiotensin infusion.[11] On the other hand there is evidence for qualitatively different responses to an infusion of angiotensin in the smooth muscle fibers of digital vessels among essential hypertensives, renovascular hypertensives and normal subjects.[3] Contradictory effects following stimulation of the renin-angiotensin system have been postulated by other authors.[5]

The pressor response that follows the injection of angiotensin is the algebraic sum of different factors. In view of the complexity and lack of precise definition of the action of angiotensin it is not surprising that we were not able to demonstrate in our series a consistent differential pattern of response.

Three possible objections to our method of study were considered and found insignificant for the following reasons: (i) the uniformity in the response of the control group could serve as evidence for the uniformity of the pressor stimulus used; (ii) the difference in mean age between the control and the other two groups is considerable but the conclusions of this paper can be drawn by statistical analysis of groups 1 and 2 alone, and (iii) in contrast with other series, the renovascular group includes only patients who had surgical cure of the renovascular hypertension at a later date.

Summary and Conclusions

The pressor response to an infusion of angiotensin II was studied in three groups of patients (renovascular hypertensives, essential hypertensives and a control group). Statistical analysis shows that the difference in pressor response among renovascular and essential hypertensives does not allow for their separation into two different groups. We conclude that under practical clinical circumstances angiotensin infusion will not serve as an adequate screening test for the identification of renovascular hypertension.

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